

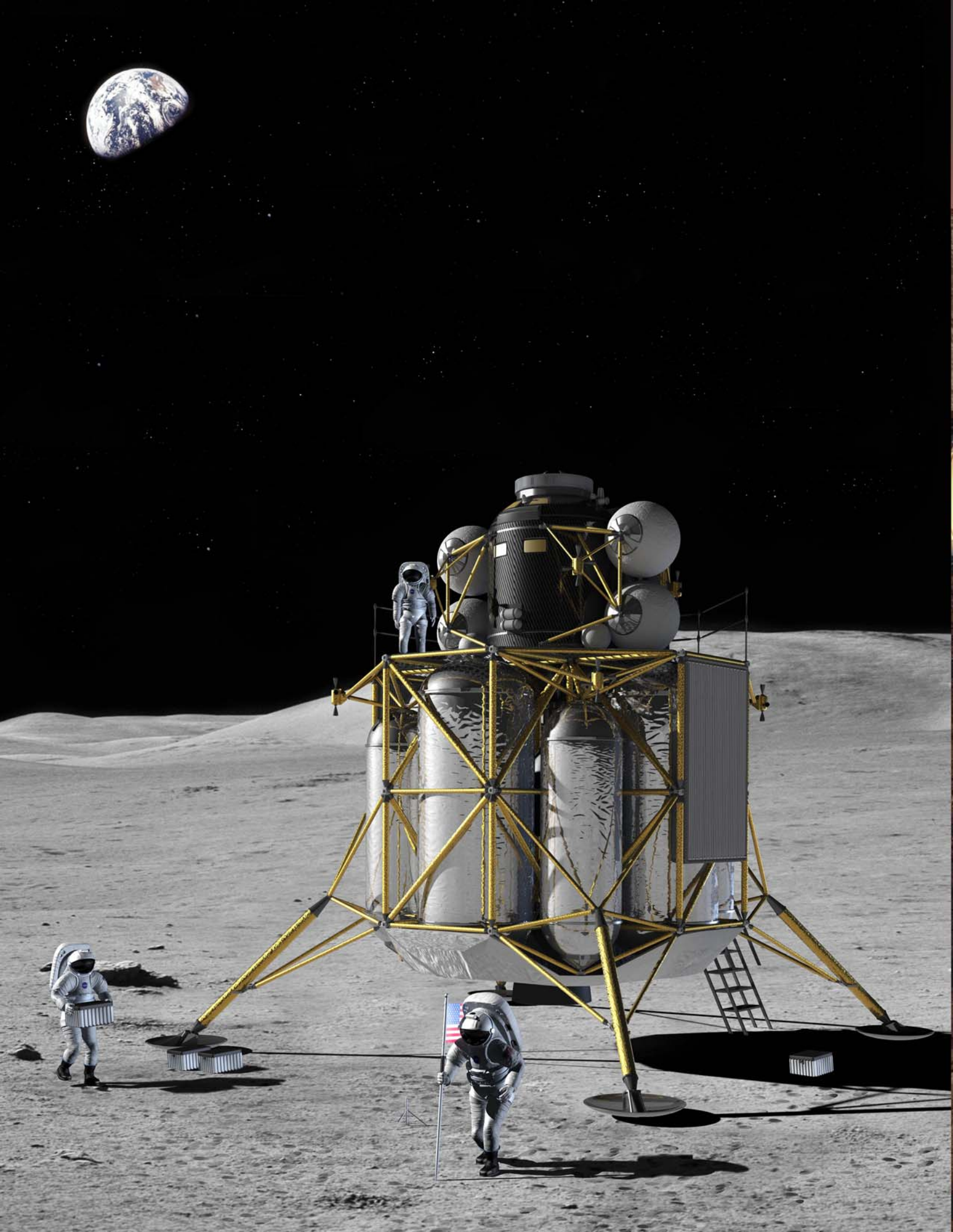
National Aeronautics and Space Administration



The John Glenn Biomedical Engineering Consortium

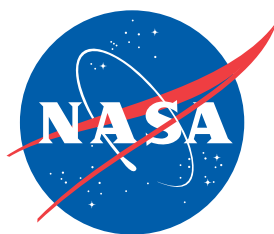


A Success Story for NASA
and Northeast Ohio



The John Glenn Biomedical Engineering Consortium

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National Aeronautics and
Space Administration



Hardware Systems Developed and Human Testing Conducted

Portable Unit for Metabolic Analysis (PUMA)

Principal Investigator: Daniel L. Dietrich, Ph.D., GRC

Co-Investigators: Nancy D. Piltch, Ph.D., GRC

Marco E. Cabrera, Ph.D., CWRU

Peter M. Struk, Ph.D., NCSE

Richard D. Pettegrew, Ph.D., NCSE

Project Rescue for Diagnosis and Treatment of Cardiac Dysrhythmias

Principal Investigator: David W. York, GRC

Co-Investigator: David S. Rosenbaum, M.D., CWRU, MetroHealth System

Chief Engineer: Michael A. Mackin, GRC

A Dual-Track Actuated Treadmill in a Virtual Reality Environment: A Countermeasure for Neurovestibular Adaptation in Microgravity

Principal Investigators: Susan E. D'Andrea, Ph.D., Cleveland Clinic

Brian Davis, Ph.D., Cleveland Clinic

Co-Investigator: Jay G. Horowitz, Ph.D., GRC

Exercise Prescription Monitoring and Feedback for Bone Mass Maintenance

Principal Investigator: Gail P. Perusek, GRC

Co-Investigators: Brad Humphreys, ZIN Technologies

Marcus Just, ZIN Technologies

Carlos Grodzinski, Ph.D., ZIN Technologies

Peter R. Cavanaugh, Ph.D., D. Sc., Cleveland Clinic

A Harness for Use With Exercise Countermeasures

Principal Investigator: Peter R. Cavanaugh, Ph.D., D.Sc., Cleveland Clinic

Co-Investigators: Gail Perusek, GRC

Carlos Grodzinski, Ph.D., ZIN Technologies

Developing Unique Monitoring Devices

Integrating Noninvasive Technologies to Enable Effective Countermeasures During Prolonged Space Travel

Principal Investigator: Rafat R. Ansari, Ph.D., GRC

Co-Investigator: Marco E. Cabrera, Ph.D., CWRU

Sliver Sensor: A Microminiature Monitor for Vital Electrolyte and Metabolite Levels With Adaptability, Self-Checking Capability, and Negligible Power Requirements

Principal Investigator: Miklos Gratzl, Ph.D., CWRU

Co-Investigator: Koji Tohda, Ph.D., CWRU

In Vivo Bioluminescent Molecular Imaging With Application to the Study of Secretory Clusterin, a Potential Biosensor During Space Exploration

Principal Investigator: David L. Wilson, Ph.D., CWRU

Co-Investigators: David A. Boothman, Ph.D., UHCCM, CWRU

Andrew Rollins, Ph.D., CWRU

A MicroSensor Array for Exercise and Health Monitoring

Principal Investigator: Gary W. Hunter, Ph.D. GRC

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Darby Makel, Ph.D., Makel Engineering, Inc.

Benjamin J. Ward, Ph.D., Makel Engineering, Inc.

A High-Resolution Portable Ultrasonic Imaging System

Principal Investigator: Shuvo Roy, Ph.D., Cleveland Clinic

Co-Investigators: Aaron Fleischman, Ph.D., Cleveland Clinic

Noel Nemeth, Ph.D., GRC

Ken Goldman, Ph.D., H-Cubed, Inc.

New Techniques and Devices

Development of a Recompression Chamber to Prevent Bone Loss in Space Through Exogenous Application of Acoustic Energy

Principal Investigator: Ulf Knothe, M.D., D. Sc., Cleveland Clinic

Co-Investigators: Dwight Davey, Ph.D., CWRU

Melissa Knothe Tate, Ph.D., CWRU

Two-Photon Microscopy for the Assessment of Countermeasures in Bone Loss

Principal Investigator: Greg A. Zimmerli, Ph.D., GRC

Co-Investigators: David G. Fischer, Ph.D., GRC

Marius Asipauskas, Ph.D., NCSE

Melissa Knothe Tate, Ph.D., CWRU

Controlled-Release Microsystems for Pharmacological Agent Delivery

Principal Investigator: Shuvo Roy, Ph.D., Cleveland Clinic

Co-Investigators: Aaron Fleischman, Ph.D., Cleveland Clinic

Christian Zorman, Ph.D., CWRU

Noel Nemeth, Ph.D., GRC

David Jacqmin, Ph.D., GRC

Rapid Design and Simulation Tools for Space-Bound Biochip Devices

Principal Investigator: Arnon Chait, Ph.D., GRC

Co-Investigators: Emily Nelson, Ph.D., GRC

David Jacqmin, Ph.D., GRC

Mohammad Kassefi, Ph.D., NCSE

Charles Panzarella, Ph.D., OAI

Marianne Zlatkowski, Ph.D., CWRU

The Vision and Plan

The John Glenn Biomedical Engineering Consortium was established by NASA in 2002 to formulate and implement an integrated, interdisciplinary research program to address risks faced by astronauts during long-duration space missions.

The consortium comprises a preeminent team of Northeast Ohio institutions that includes the following:

- Case Western Reserve University (CWRU) offers a Biomedical Engineering program that is one of the top programs in the nation. MetroHealth Medical Center in Cleveland is part of the consortium through its affiliation with the CWRU School of Medicine.
- The Cleveland Clinic excels as one of the top hospitals in the nation and has ranked number one in cardiac care in the United States for the past 14 years. The Clinic's Lerner Research Institute provides laboratory-based, translational and clinical research aimed at understanding the underlying causes of human diseases and developing new treatments and cures.
- University Hospitals Case Medical Center (UHCMC) ranks nationally in numerous specialties with a rich history filled with medical innovation, leading-edge research, teaching, and a bedrock commitment to outstanding patient care.
- The National Center for Space Exploration Research (NCSER) demonstrates superior capabilities in fluid physics, computational simulation, and instrumentation.
- NASA's Glenn Research Center (GRC) has outstanding competency in interdisciplinary bioengineering for human systems along with exceptional spaceflight hardware development, sensors, diagnostics, and computational modeling expertise.

The consortium provides an outstanding team of researchers, world-class clinicians, and experts in spaceflight hardware development to address critical issues affecting the health, safety, and effective performance of astronauts. The consortium is focused on biomedical research and technology development projects in fluid physics, sensors, diagnostics, and exercise systems that effectively utilize the unique skills, capabilities, and facilities of the consortium members.

Almost all of the projects initially selected involved collaboration among the consortium institutions, which ensured that the best capabilities of the consortium members were utilized in conducting the research. All of the projects selected for funding have been completed. Because of the success of the consortium projects, both for NASA and terrestrial medicine, the member institutions have extended the original agreement to continue this highly effective research collaboration through 2011.

The Results

The projects of the John Glenn Biomedical Engineering Consortium ranged from the development of hardware systems and testing with human subjects, to novel devices and diagnostic instrumentation, to research for the future development of advanced technology devices. Some of the key results of the research are discussed.

Portable Unit for Metabolic Analysis (PUMA)

It is critical to keep astronauts safe, healthy, and physically fit during long-duration missions. Metabolic monitoring of astronauts can provide essential data during activities including exercise and extravehicular activity (EVA). PUMA measures the six key quantities (oxygen, carbon dioxide, flow, temperature, pressure, and heart rate) needed to evaluate human metabolic function. PUMA is a battery-powered, self-contained device capable of measuring metabolic function at rest, during exercise, in clinical settings, or in the field. Human subject testing was conducted through a series of tests at the exercise physiology laboratories located at UHCMC and at NASA's Johnson Space Center, which validated its performance. NASA applications may include the use of PUMA's sensor technology in EVA suit design for lunar missions. Numerous opportunities exist for application to improve health care on Earth where basic physiological measurements are required including occupational fitness evaluations and training as well as dietary, nutrition, weight loss, and exercise studies.



PUMA headgear (Credit: D. Dietrich, NASA GRC).

Project Rescue

Serious cardiac rhythm disturbances have been recorded on several occasions during spaceflight. Cardiac dysrhythmia may pose a risk during long-duration spaceflight and is therefore being addressed by NASA's Human Research Program. Project Rescue developed a system of prototype hardware and software to aid in the detection and diagnosis of serious cardiac dysrhythmia. The system includes the capability to capture and display near real-time electrocardiogram (ECG) data locally (e.g., onboard a spacecraft) and remotely (e.g., on Earth). A team from

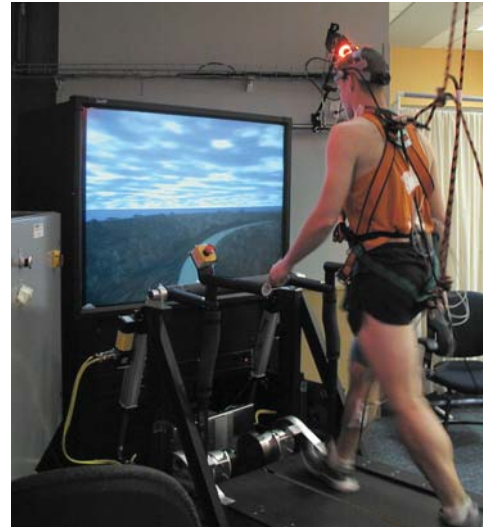


Researchers will test this prototype of the heart monitoring system for ambulatory patients with arrhythmia symptoms (Credit: NASA).

MetroHealth worked with NASA personnel to establish appropriate protocols and research objectives. A series of human subject tests was conducted in the simulated microgravity environment onboard the KC-135 research aircraft. Analysis of the test data by MetroHealth confirmed that Project Rescue hardware provides accurate data during microgravity flight. Based on the project's success, clinical trials of the technology were initiated by MetroHealth and there is significant commercial interest in applying this technology to health care on Earth.

Dual Track Treadmill With Virtual Reality

The neurovestibular system is primarily responsible for balance and stabilization. The microgravity environment alters the cues given to the human neurovestibular system, resulting in sensory conflicts during reentry and post flight. This can cause crew members to suffer from disabling vertigo, sudden loss of orientation, and other effects. Countermeasures are needed to eliminate these effects and assure crew safety and performance. A sophisticated Dual Track Treadmill with Virtual Reality was developed to potentially mitigate the harmful effects resulting from exposure to microgravity. Extensive instrumentation was utilized in rigorous biomechanical testing that involved 24 human subjects. Test results demonstrated the potential for the dual track, actuated treadmill device to help alleviate the postural and balance disturbances after exposure to microgravity. In addition to benefiting NASA's exploration missions, this instrumented treadmill could be an effective tool for rehabilitating patients on Earth suffering from balance disorder or other problems involving the neurovestibular system.



Subject on Dual Track Treadmill with Virtual Reality
(Credit: Cleveland Clinic).

Exercise Prescription Monitoring and Feedback for Bone Mass Maintenance

In space, astronauts exercise to counteract the detrimental physiological effects of spaceflight, including bone loss. The skeletal system adapts to mechanical loading by the “adaptive remodeling response.” When mechanical loading is diminished, as during spaceflight, significant bone loss is observed in weight-bearing skeletal locations. Astronaut exercise prescriptions do not currently employ biometrics for quantifying accumulated mechanical loads in space during exercise, nor are astronauts monitored to evaluate actual versus prescribed dosage. The Exercise Prescription Monitoring and Feedback for Bone Mass Maintenance Project developed an algorithm based on the daily load stimulus model to actively measure dosage and provide feedback to the subject in real time. Results were demonstrated through human subject testing on



The enhanced Zero-Gravity Locomotion Simulator at NASA Glenn
(Credit: NASA).

the enhanced Zero-Gravity Locomotion Simulator at NASA Glenn. The outcome is a highly practical monitoring algorithm for prescribing daily load stimulus through quantifying foot reaction force. Using this approach, exercise sessions can be optimized and overall bone loss may be reduced. The results may be applied to health care on Earth such as physical activity monitoring and osteoporosis prevention.

A Harness for Use With Exercise Countermeasures

Treadmill exercise has been used on orbit since early space shuttle flights because it has the potential to simultaneously benefit the neurovestibular, musculoskeletal, and cardiovascular systems. A treadmill with vibration isolation (TVIS) has been a major component of the exercise hardware on the International Space Station (ISS). However, it has not proven to be a successful countermeasure to address bone loss, a major concern for exploration missions. The key to the success of load-bearing exercise in space, such as treadmill running, is the application of loads to the crew member to replace gravity. The harness holding the astronaut is a key element in the overall system. ISS crew members frequently report discomfort from the current types of exercise harnesses, which makes the exercise protocols less effective. A Harness for Use with Exercise Countermeasures is an advanced, more comfortable harness utilizing insights from the backpack industry. It significantly reduces spinal column loads and better distributes loads to accommodate for individual differences, including gender. As a result, astronauts who have used the treadmill on ISS report that the ground prototype is much more comfortable than the current flight version. The harness is now being developed for flight testing on the ISS.



Prototype harness developed under the John Glenn Biomedical Engineering Consortium (Credit: NASA).



Center for Space Medicine harness trainer.

Integrating Noninvasive Technologies to Enable Effective Countermeasures

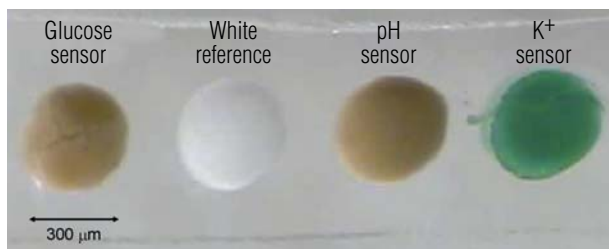
Effective monitoring of astronaut health and the early detection of potential issues are critical for long-duration space missions. The Integrating Noninvasive Technologies to Enable Effective Countermeasures Project investigated the development of optical sensors for noninvasive, quantitative medical evaluations of the eyes, skin, and brain. These sensors could ultimately be integrated into a head-mounted device for monitoring and evaluating astronaut health, similar to a pair of goggles. The device would be equipped with a suite of optical bio-sensors to address astronaut health concerns including early detection of cataracts, glucose monitoring, and changes in blood flow in the eye while under reduced gravity. Tests were conducted on human subjects and on the KC-135 microgravity research aircraft. Efforts included continuing work on a technology for early cataract detection developed and validated for clinical use at the National Institutes of Health (NIH). This technology is being used in clinical trials of anticataract drugs. The glucose monitoring sensor may be used to manage diabetes and other systemic diseases on the ground. The blood flow meter has been adapted for measuring blood flow in finger tips to study the causes of injury to an astronaut's fingers during extravehicular activity.



Space goggles being developed to monitor astronaut health.

Sliver Sensor

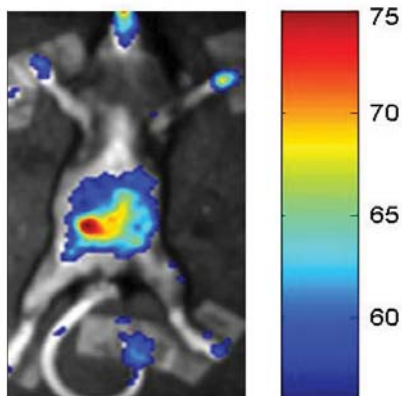
Understanding changes in human physiology during space missions is important to maintaining astronaut health and safety. The Sliver Sensor is a novel device that was conceived, developed, and tested for in vivo monitoring of glucose and electrolytes of astronauts during spaceflight. In addition to increasing basic understanding of metabolic changes in space, the device could also be critical in identifying and handling certain medical emergencies. The minimally invasive, microminiature Sliver Sensor is placed under the skin. Individual optical sensing capsules within the device change color with changes in concentration of glucose and basic electrolytes. The changes in color are read by an external watch-like device. On Earth, the device can be used to monitor electrolytes in the blood of critically ill patients and for diabetes management. In vivo testing of the device will be completed through an award from the Coulter-Case Translational Research Partnership.



An optical glucose, pH and K⁺ sensor together with optical white reference (Credit: K. Tohda/M. Gratzl).

In Vivo Bioluminescent Molecular Imaging Device

Assuring that crews can live and work safely in the radiation environment of space during extended missions is vital for human exploration. A key element of maintaining astronaut health is the development of technology to monitor the effects of space radiation on astronauts. An In Vivo Molecular Imaging Device for Measurement of Radiation Effects was developed for measuring radiation exposure. The project team successfully constructed an imaging-based, biological



In vivo imaging of transgenic mouse (Credit: CWRU).

radiation dosimeter using a reporter to produce a specific protein. Using this unique imaging instrument, the team performed cellular and animal testing to show that the bioluminescence signal responded to radiation exposure in a predictable way. This demonstrated the potential for future development of a new class of instruments to measure the effects of space radiation on astronauts. This imaging instrument helped gather critical preliminary data for large infrastructure and conventional research proposals. The consortium award was an important cornerstone for obtaining a series of successful proposals totaling more than \$11 million, which stimulated substantial growth within the CWRU imaging program. In

addition, there have been publications and research awards from NIH that were made possible with this device. The instrument was also the first in vivo molecular imaging device for small animals demonstrated in Northeast Ohio.

MicroSensor Array for Exercise and Health Monitoring

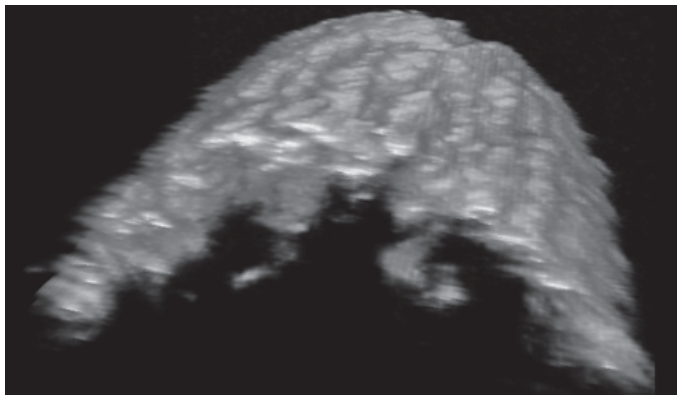
The MicroSensor Array for Exercise and Health Monitoring Project developed a miniaturized metabolic gas monitor system for use in astronaut feedback during exercise and in astronaut health monitoring. The project team fabricated and tested an integrated breath-monitoring sensor system that included an array of gas microsenors, a data acquisition and display unit, a sample pump, and a mouthpiece. Carbon dioxide and oxygen were monitored along with other gases. Team members at Makel Engineering, Inc. and the Cleveland Clinic completed significant miniaturization of the testing system and performed complete system characterization, including patient testing. Testing demonstrated that high-temperature oxygen and carbon dioxide sensors provide the functionality required for a breath monitoring system. The results outline a system for exercise feedback and personal health monitoring for use on Earth or in space. The type of sensor system developed through this project may be used in the future as a replacement for the traditional lab rack-sized equipment currently used. The collaboration established through this project led to a recent State of Ohio Third Frontier Award to develop a breath sensor system (starting with nitrogen oxide measurements) for home health applications that focus on asthma patients. This involves the Cleveland Clinic, Makel Engineering, Ohio State University, and CWRU.



Breath sensor system.

High-Resolution Portable Ultrasonic Imaging System

Developing small ultrasonic imaging systems is important to diagnose skin and bone problems in space because other imaging technologies are not compatible with spaceflight. Therefore, a High-Resolution Portable Ultrasonic Imaging System was developed. Specific bone conditions of interest included bone loss and fracture detection. The system utilizes 4-mm-diameter polyvinylidene-fluoride- (PVDF) focused ultrasonic microtransducers. High-resolution imaging of human bone was successfully demonstrated using this system. The bone was scanned in increments of 0.1 mm using a high-precision motorized stage. Visualization techniques were utilized to produce three-dimensional volume rendering of the images. Overall, the technical accomplishments have established the feasibility of ultrasound imaging for examining bone microstructure. With additional development, the PVDF microtransducers can be integrated into a portable ultrasound imaging system, which can be applied to the diagnosis of fractures and bone loss in astronauts on space missions. On Earth, the availability of portable ultrasound systems can enhance clinical diagnosis for application in remote telemedicine. The focused ultrasonic transducer has also been used to examine coronary tissue with high-resolution for advanced plaque detection and characterization. Two large medical device companies are currently engaged in license discussions for potential commercialization of the transducer design/manufacturing for intravascular ultrasound imaging applications.



Volume renderings of the ultrasound three-dimensional image (external)
(Credit: Cleveland Clinic).

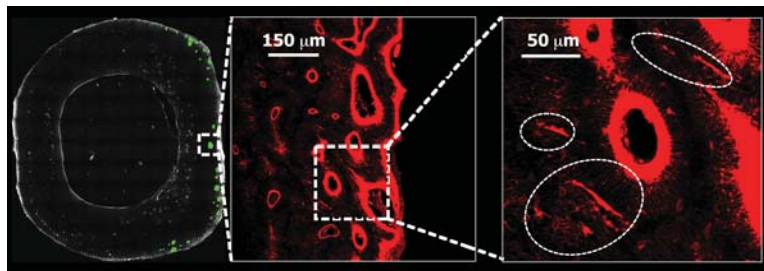


Ultrasound hardware medical imaging device currently available on the ISS (Credit: NASA).

Development of a Recompression Chamber Using Acoustic Energy to Prevent Loss of Bone

Developing countermeasures to prevent bone loss due to exposure to microgravity is a high priority in reducing risk for human spaceflight. The Development of a “Recompression Chamber” Using Acoustic Energy to Prevent Loss of Bone Project investigated the prevention of bone loss through the application of acoustic energy. Studies were conducted on sheep bone samples and on an ex vivo rat model to determine the appropriate acoustic energy parameters to mimic effects occurring naturally through physiologic activity. Tests using these results were then conducted on rats in vivo, which showed that the application of the acoustic energy triggered responses favorable to healthy bone growth. Finally, rats were exposed to acoustic energy to evaluate the effectiveness of acoustic shock waves in counteracting bone loss due to simulated microgravity. Results showed, for the first time, that utilization of acoustic energy is a potential therapy to prevent bone loss associated with exposure to microgravity. This technique could also be used

to prevent bone loss on Earth due to inactivity. Interest has been shown in exploring a commercial application of the technique to prevent and combat osteopenia (low bone mineral density).



Microdamage throughout the cortex of the cross section resulting from application of acoustic energy to cortical bone blocks (Credit: Tami et al.).

Fluorescent Microscopy Technique

Bone loss in weight-bearing skeletal locations during long-duration spaceflight is a serious issue for astronauts. Data from NASA's past crewed missions indicates that astronauts experience a significant reduction in bone mass density (BMD) due to exposure to microgravity. Because it is dense and optically opaque, bone tissue is a particularly challenging subject for white light imaging or fluorescence microscopy. A novel Two-Photon Microscopy Technique, which uses a custom-built two-photon microscope, was tested on frozen human femur and tibia bone samples. The new images were compared to those captured using a conventional confocal microscope. The two-photon imaging technique showed distinct advantages in image quality when penetrating deeper into the bone tissue. It also manifested better imaging depth and improved spectral resolution characteristics. The results demonstrated the benefits of using two-photon microscopy to understand the underlying mechanisms of bone changes in astronauts and humans on Earth. In addition, the project team conducted research to better understand in vitro cell cultures and the regulation of expressed proteins, which may be used to develop countermeasures for space-induced bone loss.

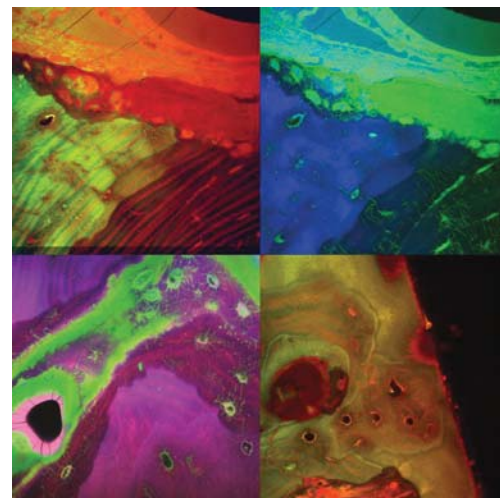
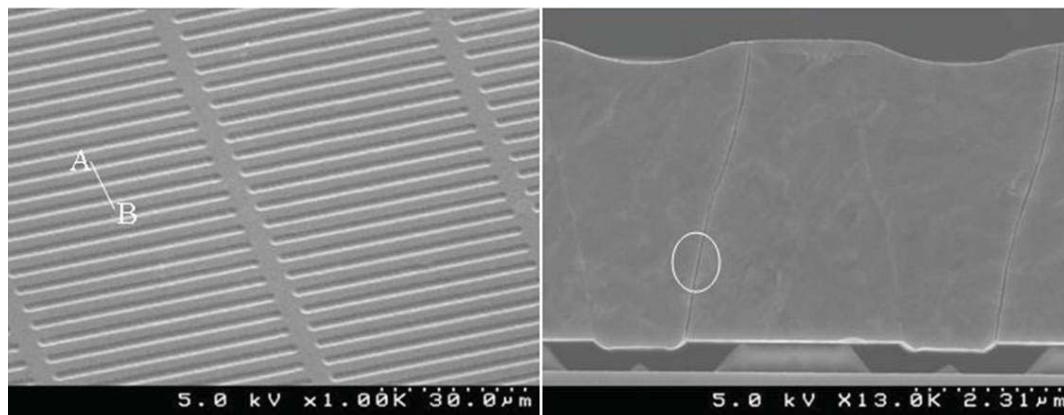


Image gallery of spectrally resolved, false color, two-photon images of bone tissue stained with basic fuchsin.

Microsystem for Controlled Continuous Drug Delivery

Effectively administering pharmacological agents is a key capability needed to ensure the health of astronauts during space missions. Miniature, implantable microsystems for the controlled release of pharmacological agents offer the potential for research investigations into health problems of astronauts as well as for their immediate treatment. The Microsystem for Controlled Continuous Drug Delivery is based on diffusion through nanoporous membranes that are fabricated using microelectromechanical system (MEMS) techniques. Diffusion through the porous membrane can be designed to achieve different rates of release for a given pharmacological agent. Continuous drug delivery through a slow infusion while maintaining the right therapeutic concentration of the drug in the patient's body enables better control and eliminates the need for repeated injections. The project established the feasibility of developing silicon nanoporous membranes for use in controlled release microsystems. The underlying technology from this project has potential for use in ultrafiltration applications such as generating medical grade water and in developing a bio-artificial kidney that can be used instead of dialysis. The kidney project has been funded through a recent NIH 3-year grant to the Cleveland Clinic.



Top- and cross-sectional view of a nanoporous membrane matrix (Credit: Cleveland Clinic).

Rapid Design and Simulation Tools for Space-Bound Biochip Devices

A biochip is a collection of miniaturized test sites on a surface area usually smaller than a fingernail. The test sites, or microarrays, can perform many biological tests at the same time. A biochip can quickly perform thousands of biological reactions. Biochips could provide unique, miniaturized onboard diagnostic systems and treatment devices for long-duration NASA missions. However, there are significant challenges when using biochips in a microgravity environment. The Rapid Design and Simulation Tools for Space-Bound Biochip Devices Project developed a numerical simulation environment for customizing and optimizing biochips for microgravity operations. Microgravity-unique physics and biological sensing requirements were investigated. Customized codes were developed in house for specific microgravity physics effects. Numerous studies encompassing biochips and microgravity operations were completed and generalized tools were developed.

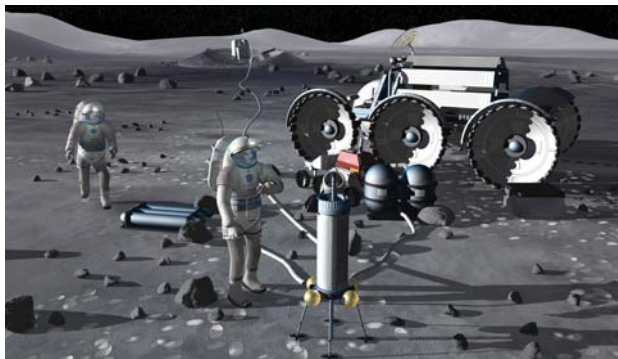


Nanogen's DNA/RNA electrically addressable microarray (Credit: Nanogen, Inc., San Diego, CA).

The Outcome

The John Glenn Biomedical Engineering Consortium projects have provided significant contributions to NASA by developing technologies to address critical risks affecting the safety, health, and performance of astronauts during long-duration space missions. The projects have developed new diagnostic devices and potential methods for reducing the harmful effects of exposure to space. The consortium has also served as a pathfinder and model for interdisciplinary, multi-institution collaboration. Additional collaborations have resulted from the successful experiences of the consortium. The consortium has served as a cornerstone for establishing NASA Glenn and Northeast Ohio as an integral part of NASA's Human Research Program.

In addition to the benefits to NASA, many of the devices and techniques investigated may improve health care on Earth. There has been significant interest in commercializing products from a number of projects, potentially contributing directly to economic development in the biosciences, a major priority for Ohio's Northeast region. The John Glenn Biomedical Engineering Consortium continues to contribute to NASA's mission and the vitality of Northeast Ohio.







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